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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
LUCAS, ZACHARIAH

ART UNIT	PAPER NUMBER
1648	

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6

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/485,099	Applicant(s) FRACE ET AL.	
	Examiner Zachariah Lucas	Art Unit 1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondenc address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-84 and 90-94* is/are pending in the application.

4a) Of the above claim(s) *24-84* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *90-94* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Currently, claims 24-84, and 90-94 are pending in the application. In the restriction requirement, as indicated by the Applicant, the Examiner requested that the Applicant amend certain claims of the Application. The purpose of this request was so that the application file would clearly reflect the claims in the application at present. Such has been done by the Applicant's submission of the amended claim set. The Examiner appreciates the Applicant's cooperation.

Election/Restrictions

2. Applicant's election of Group IV in Paper No. 5 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

3. Claims 24-84 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 5.

Priority

4. An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification of in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior

nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number. Also, the current status of all nonprovisional parent applications referenced should be included.

Examiner Query

5. It is noted that the Applicant may act as his or her own lexicographer to specifically define a term of a claim contrary to its ordinary meaning. In the present case, the Applicant appears to use the term "transmembrane region" in claims 90 and 93 to mean the region of the viral protein encompassing residues 26-43 of the sequence (page 3, lines 21-23). However, in the art, the accepted region of the transmembrane regions appears to comprise residues 25-43. See e.g., Tosteson et al. (J Membrane Biol 142: 117-126, page 118, Figure 1A- of record in the IDS); Watanbe et al. (J Virol 75(12): 5656-5662, page 5657, Figure 1); and Black et al. (J Gen Virol, 74: 1673-77, page 1673, right column- of record in the IDS). Confirmation that the Applicant is defining the term "transmembrane region" as consisting of residues 26-43 is requested.

Claim Objections

6. Claim 93 is objected to because of the following informalities: The claim is an independent claim. However, the claim beings with the phrase "The method of preparing an M2 antibody..." Because the claim is an independent claim, and because the claimed method has not been previously introduced, the claim should read "A method of preparing an M2 antibody..." Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 90-94 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 90 will be treated as representative of the rejected claims. This claim reads on a method "of preparing an M2 antibody" comprising immunizing an animal with a composition comprising a M2 polypeptide and a pharmaceutical carrier. The claims are being rejected because it is unclear what the term "preparing" is intended to convey. As written, the claims read on methods of inducing antibody production in an animal. However, as no further processing or isolation of the antibodies is involved in the claimed inventions, there does not appear to be any "preparation" of the antibodies beyond inducing their creation.

9. Claims 93 and 94 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 93 recites the limitation "The method of preparing an M2 antibody, the method comprising..." in line 1 of the claim. There is insufficient antecedent basis for this limitation in the claim. It is not clear to which method the claim is referring.

10. Claims 90-94 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described

in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims read on methods of raising antibodies to any M2 polypeptide. However, while the Applicant has disclosed the making and use of an M2 polypeptide from the influenza A virus, the Applicant has not disclosed the making and use of the claimed polypeptides from other viruses to make an anti-M2 antibody.

The following quotation from section 2163 of the Manual of Patent Examination Procedure is a brief discussion of what is required in a specification to satisfy the 35 U.S.C. 112 written description requirement for a generic claim covering several distinct inventions:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus... See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.
>
> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

Thus, when a claim covers a genus of inventions the specification must provide written description support for the entire scope of the genus. Support for a genus is generally found where the applicant has provided a number of examples sufficient so that one in the art would recognize from the specification the scope of what is being claimed.

In the present case, the Applicant has described the M2 protein, and the transmembrane sequence thereof, for the influenza A virus. E.g., App., pages 1-3. Further, the Applicant has indicated that the claimed invention is drawn to polypeptides from the influenza A protein. See

e.g., page 3, lines 28-29. It is noted that the Applicant has nowhere specified that the term M2 polypeptide is limited to polypeptides derived from the M2 protein of the influenza A virus.

It is known in the art that other viruses have M2 proteins. See e.g., Srikiatkhachorn et al., J Exp Med 186: 421-32, abstract, and Wagner et al., J Virol 71: 2371-82, abstract (each disclosing other viruses with M2 proteins). Because the Applicant has not provided any indication that they were in possession of any other of the claimed M2 polypeptides than those of the influenza A virus, and because the Applicant has not provided any examples of such polypeptides other than those of influenza A, the Applicant has not provided adequate written description support for methods of raising anti-M2 antibodies to any protein other than those of the influenza A virus.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 90, 91, and 93 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kendal et al. (U.S. Patent 5,290,686) in view of Black et al. (J Gen Virol- 74: 1673-77- of record in the IDS), Spaete (U.S. Patent 5,474,914). This claim reads on methods of producing monoclonal antibodies to the M2 protein of the influenza virus comprising the administration to a subject a modified M2 polypeptide, wherein the transmembrane domain of the M2 protein has

been deleted from the polypeptide, and a pharmaceutical carrier. The polypeptides may also comprise a substitution of the transmembrane region for one or more neutral or hydrophilic amino residues.

Kendal teaches a method of making and using a vaccine to the influenza A virus comprising recombinantly producing an influenza A M2 protein in a baculovirus/ insect cell expression system. See, column 2, lines 53-59, and col. 3, lines 14-19. The reference also teaches that M2 protein so produced react with antibodies to the naturally occurring M2 protein, and that such proteins may be used to raise anti-influenza antibodies. See, column 6 lines 16-25, and lines 46-57. Kendal also teaches that the M2 protein is toxic to the insect cell in which it is being expressed. Col. 6, lines 7-15. However, the reference does not teach the making and use of M2 polypeptides wherein the transmembrane domain of the M2 protein has been deleted.

Black teaches that the transmembrane region of influenza the M2 protein comprises residues 25-43 of the protein sequence. The reference does not teach the deletion of this region from the protein.

Spaete teaches a method of expressing viral proteins in baculovirus/ insect cell expression systems. Columns 8-10, and 14-16. While the reference does not identify influenza antigens among the viruses for which the discloses methods may be used, the reference does indicate that the method may be applied to the production of viral proteins generally. Abstract. This, in view of the teaching of Kendal indicating that a baculovirus/ insect cell expression system may be used for M2 polypeptide expression, would have indicated to those in the art that the protein could be expressed in this system.

Spaete further teaches that, in order to facilitate secretion of the protein, and to prevent transmembrane binding, it is preferable to remove the transmembrane domain of proteins being expressed in the disclosed methods. Col. 5, lines 54-65. Further, the reference also indicates that, in the place of the transmembrane region, one may insert other hydrophilic amino residues. Col. 6, lines 14-18. Thus, each of the Kendal and Spaete references provide a reason to combine the references such that the transmembrane domain of the M2 polypeptide is deleted. Spaete to facilitate secretion from the cell, and Kendal, because retention of M2 in the cell is toxic to the cell. It would also be apparent to those in the art that, by removing the limiting factor of protein expression in the Kendal reference (the toxicity of the intracellular M2 in the cell), greater protein expression could be achieved.

It is noted that Spaete also teaches the use of a fusion of the desired protein to a protein signaling for the fusion proteins' secretion. See e.g., column 18, lines 36-49, and claim 1. However, the reference also teaches that the fusion protein preferably comprises processing sites, allowing for the cleaving off of the signaling sequence. Id., at lines 46-49. The use of such processing is known in the art. See e.g., Carter et al., Chapter 13 of *Protein Purification: From Molecular Mechanisms to Large Scale Processes*, American Chemical Society, Washington DC (1990- of record in the IDS filed on April 27, 2000). Thus, while the claims do not exclude embodiments wherein the antibodies are made through the use of a fusion protein of M2 and a secretion signal, the references render obvious embodiments both with and without such a signal.

Because Kendal both teaches the use of the polypeptide as a vaccine, and as capable of producing anti-influenza A antibodies, the references teach and suggest the use of the claimed method of making antibodies. Those in the art would have had a reasonable expectation of

success in the making of such a protein antigen because Katz et al., (Options for the control of influenza III, pp. 837-43- of record in the IDS) teaches that the antigenically reactive regions of the protein lie in the N-terminal and cytoplasmic C-terminal of the protein, and not in the transmembrane region. See, Katz, page 838, crossover paragraph from page 837). Those in the art would also have had a reasonable expectation in the application of the teachings of Spaete to the protein of Kendal because the art teaches that the desired result (loss of membrane integration) can be achieved in the M2 protein through deletion of at least 6 amino residues from the transmembrane domain. See e.g., Hull et al., J Cell Biol 106: 1489-98, abstract. One skilled in the art would therefore have had a reasonable expectation of success in the making of an immunogenic influenza M2 protein wherein the transmembrane region has been deleted.

It is noted that the references do not teach the exclusion of residues 26-43, rather residues 25-43. However, the claim language does not exclude the additional deletion of the N-terminal residue. Further, from the teachings of the above references, it would have been equally obvious to delete only residues 26-43 (leaving the additional residue in place). This is because one skilled in the art would have deemed the deletion of the majority of the transmembrane region sufficient for the expression of a soluble M2 protein.

13. Claims 90- 93 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kendal in view of Black and Spaete as applied to claim 90 above, and further in view of Anderson et al. (U.S. Patent 6,180,343). Claim 92 further limits the M2 polypeptide described above to embodiments wherein "all of the deleted amino acids are replaced with from one to six glycine residues." Anderson et al teaches that preferred linkers for fusion proteins include glycine

polymers (neutral amino acid), and glycine-serine polymers (a combination of neutral and hydrophilic amino acids). Col. 15, lines 50-59. Because these linkers are known in the art, and because practice of the methods according to the other references above would require some form of connection between the N-terminal and C-terminal regions of the M2 polypeptide, it would have been obvious to use such polymers as linkers to replace the deleted transmembrane region of the M2 protein.

14. Claim 94 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kendal in view of Black, Spaete, and Anderson as applied to claims 90-93 above, and further in view of Ito et al. (J Virol 65: 5491-98- of record in the IDS). Claim 94 further limits method of claim 93 to embodiments wherein the M2 polypeptide is derived from the native M2 protein of the influenza virus strain A/Aichi/2/68 (H3N2). The teachings of Kendal, Black, Spaete, and Anderson have been described above. Ito teaches the sequence of the M2 protein of the identified strain. See, page 5494, and 5495 (respectively, the description of Figures 2 (A) and (B), and Figure 2(B)). Because Ito teaches the sequence of the identified strain, because Kendal teaches that the M2 protein is conserved across influenza strains, and because Ito confirms the assertion, those in the art would have been motivated to use the M2 protein of any influenza strain, including the identified strain, as the immunogen in the method taught by Kendal. Thus, it would have been obvious to modify any influenza strain, including the identified strain, as indicated by the additional references.

Conclusion

15. No claims are allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 703-308-4240. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Z. Lucas
Patent Examiner

JAMES HOUSEL 9/23/03
SUPERVISORY PATENT EXAMINER
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